REMARKS

Claims 26-33, 35, and 53-74 are currently pending in the application. Claims 27-28, 31-33, 35, 54-56, 60-62, 65-66, and 72-73 are canceled. Claims 26, 53, 59, 67, and 74 are amended. The amendments find support in the specification and are discussed in the relevant sections below. No new matter is added.

Applicants wish to thank the Examiner for a telephone interview with Applicants' representatives on November 2, 2004, in which the enablement rejection was discussed. The substance of that interview is included in the following remarks.

Formal Matters

The Examiner has withdrawn the previous objection to the drawings in view of the newly submitted figures, but requests that Applicants submit a complete set of formal drawings. Applicants have filed herewith a complete set of formal drawings for the instant application.

The Examiner has also objected to the disclosure because, while the abstract has been submitted, it was not submitted on a separate sheet. The Examiner requires a new abstract of the disclosure to be provided on a separate sheet, apart from any other text. Applicants have provided herewith an abstract on a separate sheet in accordance with 37 C.F.R. §1.52(b)(4).

Rejection of Claims 26-33, 35, and 53-74 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 26-33, 35, and 53-74 under 35 U.S.C. §112, first paragraph as not being enabled for the full scope of the claimed invention. The Examiner asserts that the specification does not contain working examples that demonstrate "the effects of various inhibitors in the claimed methods either *in vitro* or *in vivo*." The Examiner asserts that undue experimentation would be required to practice the claimed invention "because it is required [sic] further research to obtain the effective amount of various inhibitors having different structures for *in vivo* inhibiting [sic] bacterial growth."

As discussed during the telephone interview, Applicants have significantly narrowed the claims of the instant invention to recite decreased bacterial growth or decreased bacterial DNA

synthesis *in vitro* only. Applicants have also amended the claims to make clear that the effect of the recited inhibitor is to either inhibit bacterial growth, or bacterial DNA synthesis. Accordingly, Applicants submit that the portions of the Examiner's rejection relating to the lack of enablement for *in vivo* treatment, and the lack of guidance as to the effect of the recited inhibitor are now moot.

According to well settled law, the enablement requirement is satisfied if, after reviewing the application, the ordinarily skilled artisan can reproduce the claimed invention without resorting to "undue experimentation." *In re Wands,* 858 F.2d 731. Moreover, "[e]nablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. 'The key word is 'undue' not 'experimentation' ' " (citing *In re Angstadt*, 537 F. 2d 498 at 504, 190 U.S.P.Q. 214 at 219 (C.C.P.A. 1976)). The *Wands* Court also stated that "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed" (citing *In re Jackson*, 217 U.S.P.Q. 804 at 807 (Bd. App. 1982)). Applicants submit that the specification provides ample guidance to permit one of skill in the art to make and use the full scope of the claimed invention without undue experimentation.

The specification establishes that *S. aureus* DnaI activity is a key pathway for bacterial growth inhibition, and that interruption of this pathway decreases bacterial growth and bacterial DNA synthesis. For example, the specification teaches that the bacteriophage protein 77ORF104 specifically binds to DnaI and fragments thereof (see Figures 12, 14, and 16), that 77ORF104 has a high killing potential when expressed in *S. aureus* (see Figure 7, and page 84, line 14 – page 85, line 2), and that, as shown in Figure 13, *S. aureus* DNA synthesis is inhibited by bacteriophage 77ORF104.

Having established that bacterial growth and DNA synthesis is inhibited by blocking the DnaI pathway with an inhibitor such as 77ORF104, the specification further teaches how one of skill in the art would use the disclosed interaction between DnaI and 77ORF104 to identify

additional inhibitors of bacterial growth and DNA synthesis. For example, the specification teaches at pages 67-78, methods and assays which may be used to identify agents which act as inhibitors of DnaI and are thus useful according to the claimed invention. The specification teaches the types of agents which one of skill in the art would likely focus on to identify an inhibitor: small organic molecules, peptides, polypeptide, and antibodies (page 68). The specification teaches that such agents can, for example, be compounds related to and variants of 77 ORF 104. Thus, one of skill in the art would readily be able to identify variants, mimetics and homologs of 77 ORF 104, and test them using the methods described in the specification (and referred to below) to determine whether such variants and homologs function as inhibitors of DnaI. The specification teaches binding-based assays to determine whether a candidate inhibitor binds to DnaI and therefore functions as a potential inhibitor of DnaI activity (see pages 70-75). The specification teaches methods for determining whether an inhibitor inhibits bacterial DNA synthesis (page 75). With respect to methods for determining whether an inhibitor inhibits bacterial growth, Applicants submit that these methods are routine in the art, as described in the working examples of the specification (see Example 1, starting on page 83). Moreover, the specification teaches on, pages 75-77, assays for determining whether a candidate inhibitor reduces the activity of DnaI. The specification defines "decreases activity", as a 10% decrease in activity of a candidate compound. Finally, the specification teaches how to screen for an inhibitor of DnaI, the criteria to be used in making a determination of whether a given compound is an inhibitor useful in the invention, and how to determine whether a given inhibitor inhibits bacterial growth, and/or bacterial DNA synthesis. Applicants submit that it would require no more than routine experimentation and/or testing to identify further inhibitors of DnaI which inhibit bacterial growth and/or bacterial DNA synthesis.

As evidence of the routine nature of using the novel DnaI/77ORF104 interaction to identify additional inhibitors of DnaI, Applicants had previously presented a Rule 132 Declaration by Dr. Jerry Pelletier. The Pelletier Declaration demonstrates identification of an additional bacteriophage inhibitor following the methods of the invention. The Declaration identified the bacteriophage protein PVLORF16 as an inhibitor of bacterial growth and bacterial DNA synthesis, and was shown to bind to DnaI. The Examiner questioned during the telephone interview whether PVLORF16 was a distinct protein from 77ORF104 or whether it was

potentially a subsequence or fragment of 77ORF104. Applicants submit that PVLORF16 is an unrelated protein from a completely different bacteriophage than 77ORF104, with almost no sequence identity between the two peptides.

In addition to the Rule 132 Declaration, Applicants cited Liu et al. (2004, Nature Biotechnology 22: 185) as teaching small molecules which were identified using the methods described in the instant specification, and which were shown to inhibit bacterial growth and bacterial DNA synthesis via inhibition of DnaI. Applicants emphasize that the inventors of the instant claims are authors *inter alia* of Liu et al. On further review of Liu et al., Applicants have determined that the reference actually teaches **a greater number** of inhibitors than originally reported to the Examiner. Liu et al. identified **36 small molecules** which were shown to inhibit the interaction between DnaI and 77ORF104. Of these, 11 were tested further and found to inhibit bacterial growth. Two of these were examined further and were identified as inhibiting DNA synthesis via DnaI. Furthermore, neither of the two compounds was significantly toxic to human primary hepatocytes or to the cell lines HepG2 and HeLa. Thus, by following the methods taught in the specification, Liu et al. was able to identify 36 small molecules inhibitors and showed inhibition of bacterial growth and/or inhibition of bacterial DNA synthesis for a significant subset of these small molecules.

The Examiner states that the specification is not enabling because it does not provide sufficient guidance as to the amounts or concentrations of an inhibitor which could be used to inhibit bacterial growth or bacterial DNA synthesis. First, the Applicants point out that the specification does provide guidance as to the amounts or concentrations of an inhibitor useful in the invention. Indeed the specification indicates at page 43, lines 4-6 that binding concentrations for two polypeptides that specifically binds another is usually in the range of about 1 μM to 10 pM or lower. Secondly, while one of skill in the art may have to test several concentrations of a particular inhibitor to determine the optimal concentration for inhibition, Applicants stress that this type of testing is routine and standard for any type of cellular assay. For instance, pages 75-76 of the specification describe an assay to screen for inhibitors of DNA replication in which varying concentrations of candidate inhibitors are tested in place of 77 ORF104. Applicants submit that it is standard practice, having identified an inhibitor, agonist, or antagonist, to

perform a dose/response or dose/inhibition curve to determine the most effective concentration of the inhibitor, agonist, or antagonist. It is not undue experimentation for one of skill in the art to perform a dose/response experiment when such an experiment is the standard practice in the art.

The specification teaches methods for inhibiting bacterial growth and bacterial DNA synthesis by inhibiting DnaI activity. The specification provides working examples of inhibition of bacterial growth, inhibition of bacterial DNA synthesis, and binding of DnaI by 77ORF104. The specification also teaches routine methods for identifying additional inhibitors which are useful for inhibiting bacterial growth and bacterial DNA synthesis. The routine nature of the experimentation needed to identify additional inhibitors is evidenced by post-filing data which teaches a further bacteriophage protein and 36 small molecules which are useful for modifying the DnaI pathway. The specification provides ample teachings to permit one of skill in the art to make and use the claimed invention without undue experimentation, and is thus enabling for the full scope of the claimed invention.

Applicants believe that the above-discussed amendments and arguments obviate the rejection of claims 26-33, 35, and 53-74 under 35 U.S.C. §112, first paragraph, and respectfully request reconsideration and withdrawal of the rejection.

Rejection of Claims 26-30 and 53-73 Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 26-30 and 53-73 under 35 U.S.C. §112, second paragraph, as being indefinite "because the claim lacks an essential step in the method of inhibiting a bacterium," namely, "the outcome of the treatment." Applicants have amended the claims to recite the "outcome of the treatment" (i.e., inhibition of "bacterial growth" or "bacterial DNA synthesis") thereby obviating the rejection. Applicants accordingly request that the rejection be reconsidered and withdrawn.

Applicants submit that in view of the foregoing remarks, all issues relevant to patentability raised in the Office Action have been addressed. Applicants respectfully request the withdrawal of rejections over the claims of the present invention.

Respectfully submitted,

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